Personalized Asthma Management: Addressing Environmental Impact

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Disclosure

Consultant for Boehringer Ingelheim, Genentech, Glaxo Smith Kline, Merck, Novartis, and Roche

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NIAID Inner City Asthma Consortium;
NIEHS/EPA Center Grant on Childhood Environmental Health;
CDPHE Colorado Cardiovascular, Cancer and Pulmonary Disease Program, Caring for Colorado Foundation.

Learning Objectives

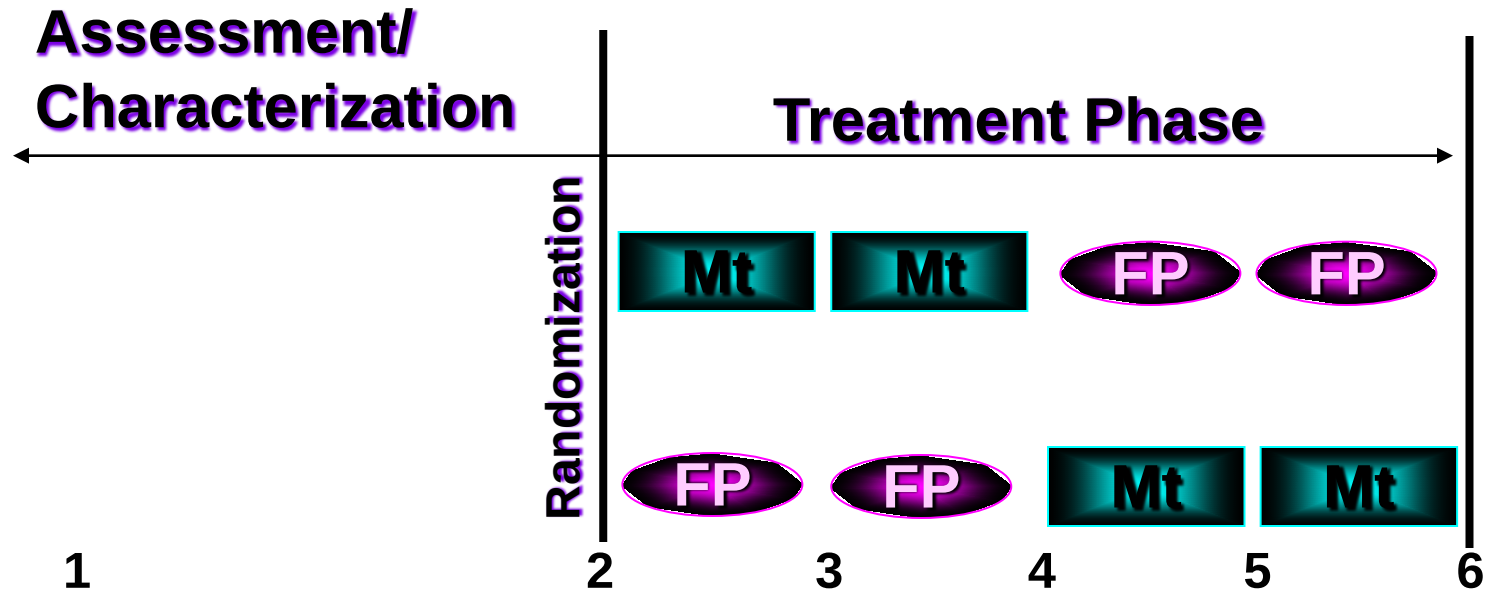
- **Identify variability in treatment response for asthma**
- **Provide insight into the role of the environment on variable treatment response**
- **Indicate the role of the CEHC in identifying environmental impact on personalized medicine.**

CLIC Study

Funded by NHLBI

Characterizing the Response
to a
Leukotriene Receptor Antagonist
and an Inhaled Corticosteroid

CLIC Study Timeline



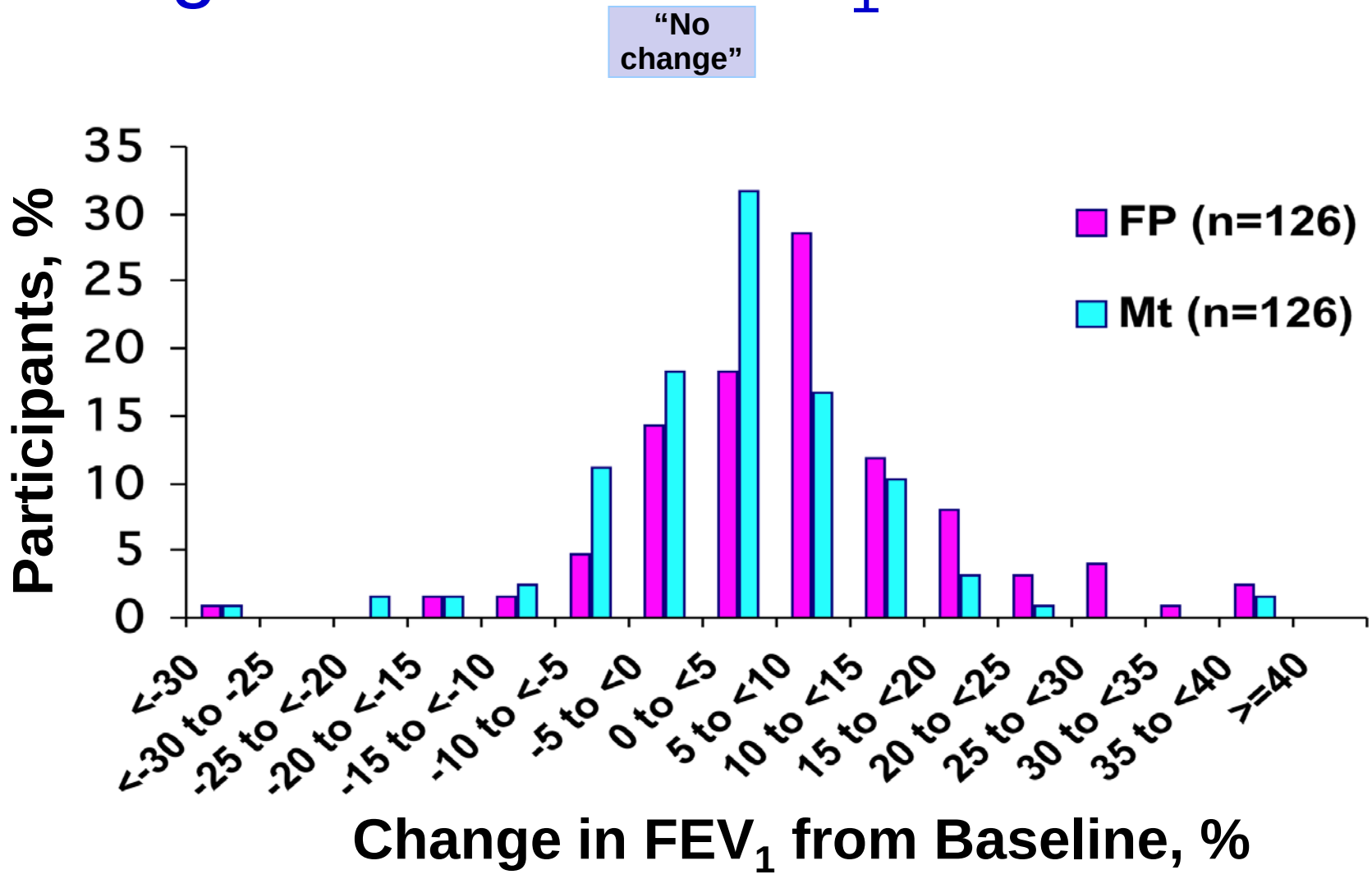
Consent
Asthma Hx
eNO
PFTs
BD response
Biomarkers
Genetics
Diary and PFM

Review diary
eNO
PFTs
Methacholine
Skin testing

Review diary
eNO
PFTs

CARE
Childhood Asthma Research & Education Network

Primary Outcome: Change in Pre-BD FEV_1



Ref. Szefler SJ and the CARE Network. *J Allergy Clin Immunol* 2005;115:233-42.

CARE
Childhood Asthma Research & Education Network

FEV_1 Response ≥ 7.5%: Odds Ratio

Baseline Characteristic (Categorical)	FP	Mt
FEV_1 < 90% predicted (pre-BD)	4.16**	1.78
FEV_1/FVC < 0.80 (pre-BD)	4.26**	2.40*
Methacholine PC_{20} ≤ 1 mg/ml	2.62*	1.17
eNO > 25 ppb	2.75*	2.03
TEC > 350 cells/mm^3	2.34*	1.62
Serum ECP > 15 μg/L	2.78**	1.18
IgE > 200 kU/L	2.86**	0.96
$uLTE_4$ > 100 pg/mg	2.03	3.22*
Female	1.14	2.30
Minority	0.84	1.98
Age ≤ 10 years	0.64	2.50*

**p ≤ 0.01; *p ≤ 0.05

Ref. Szefler SJ and the CARE Network.

***J Allergy Clin Immunol* 2005;115:233-42.**

CARE
Childhood Asthma Research & Education Network

National Jewish Health

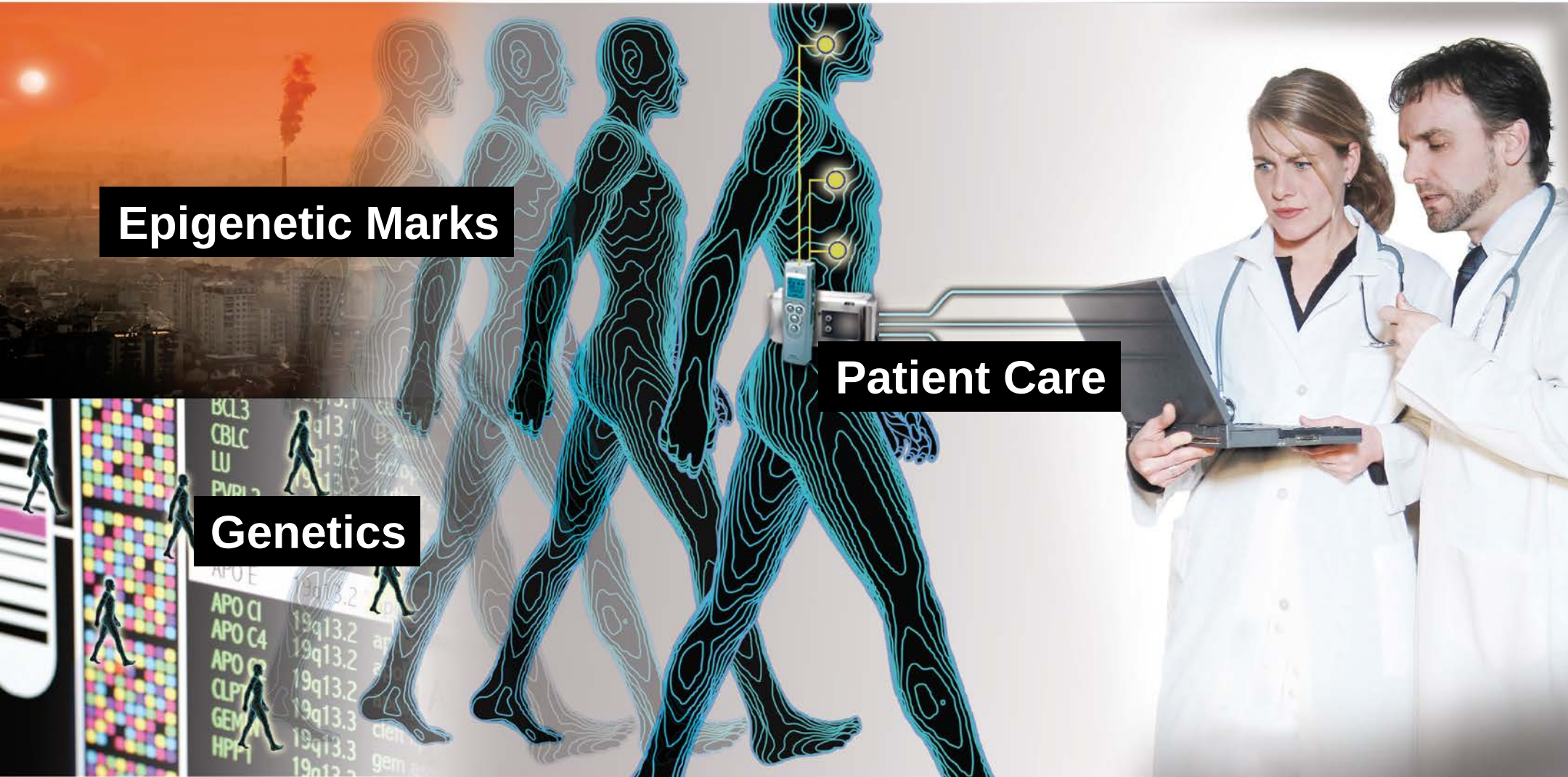
Science Transforming Life™

Genetics, Epigenetics, and Personalized Medicine

Factors Influencing Disease Onset, Severity and Effect of Therapeutic Intervention

- **Genetics** – Predisposition to disease
- **Epigenetics** – Indicator of gene-environment interaction
- **Personalized medicine** – selecting medications to reduce impact of gene-environment interaction on those predisposed to develop disease

Genetics, Epigenetics, and Personalized Medicine




15 February 2001
nature
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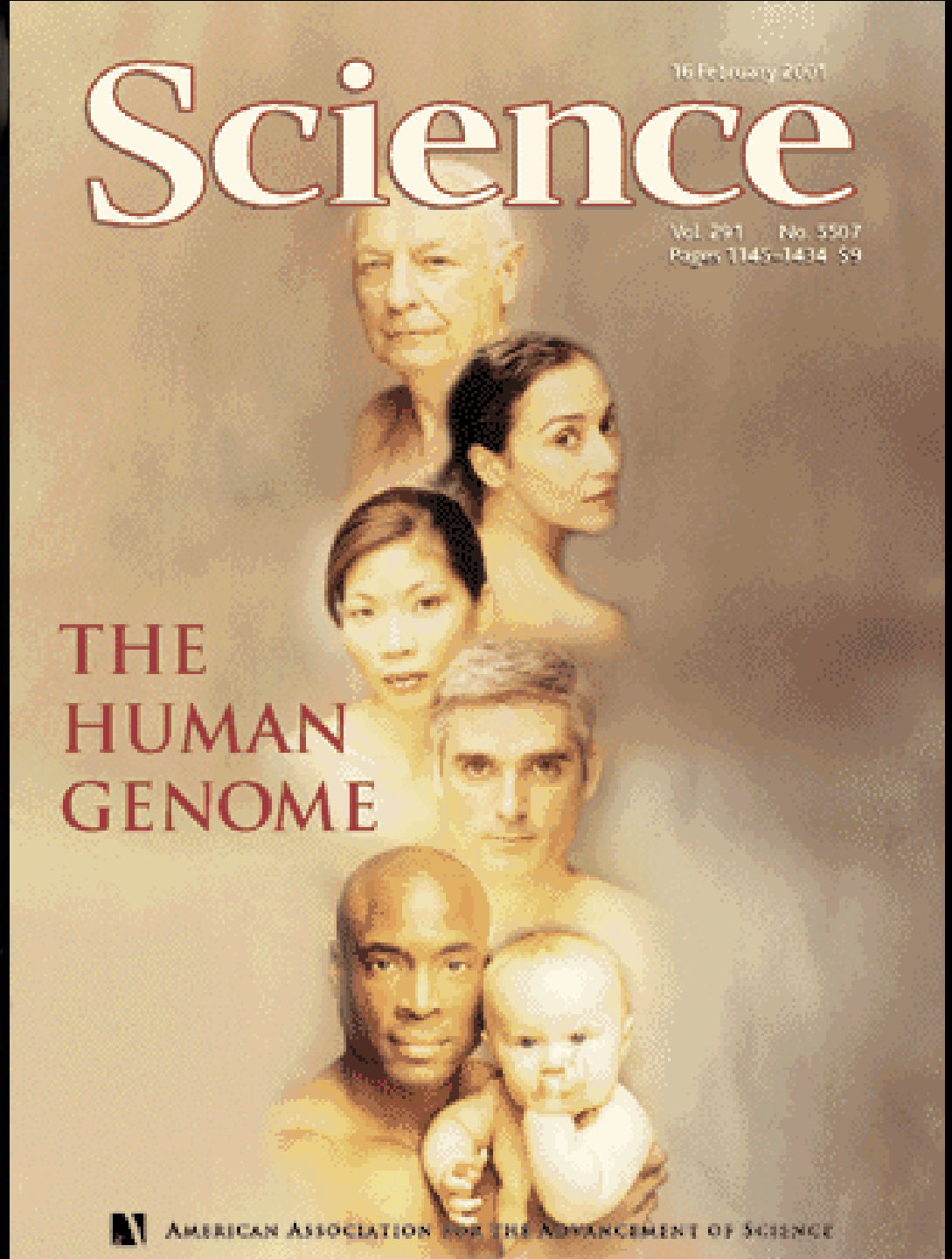
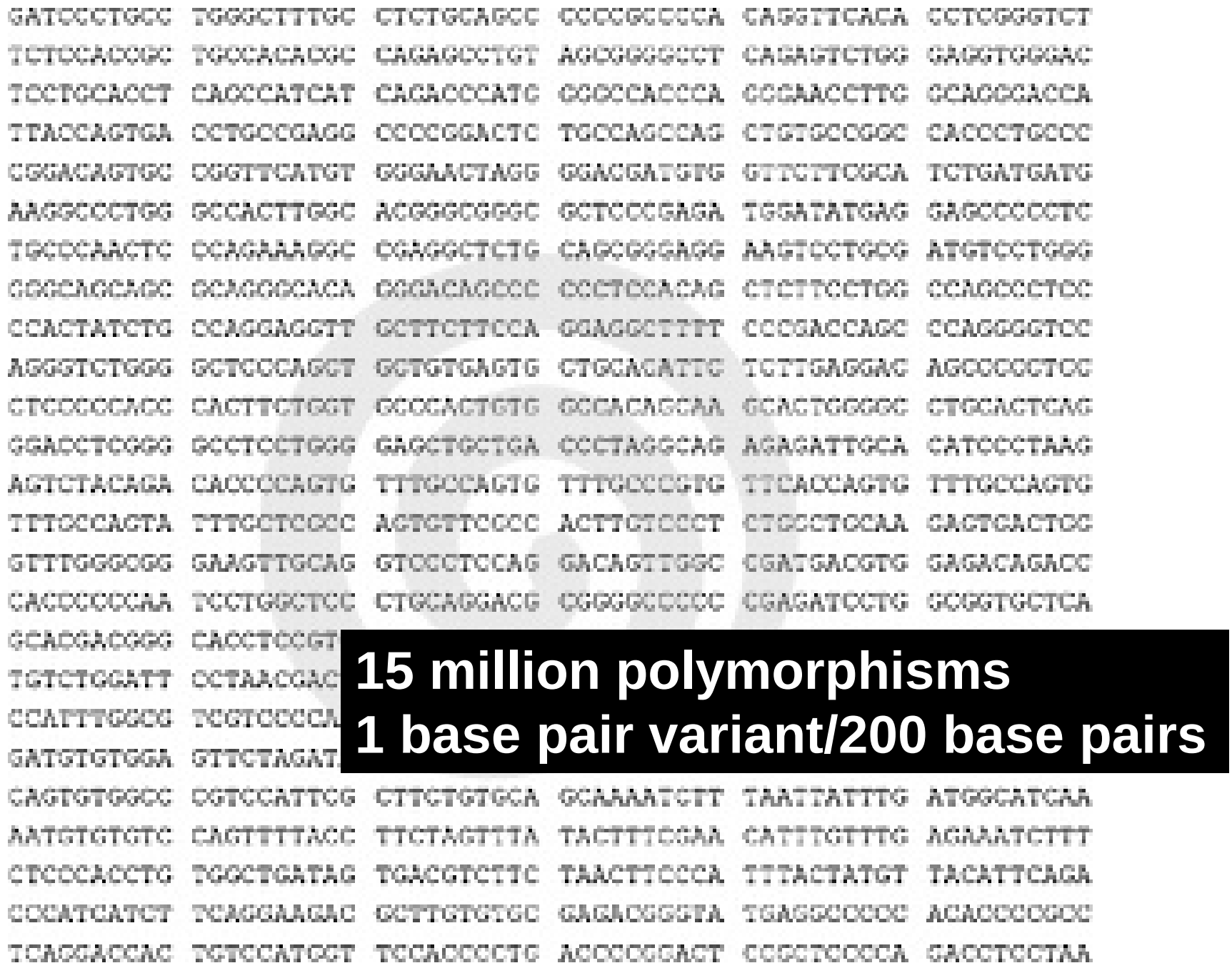
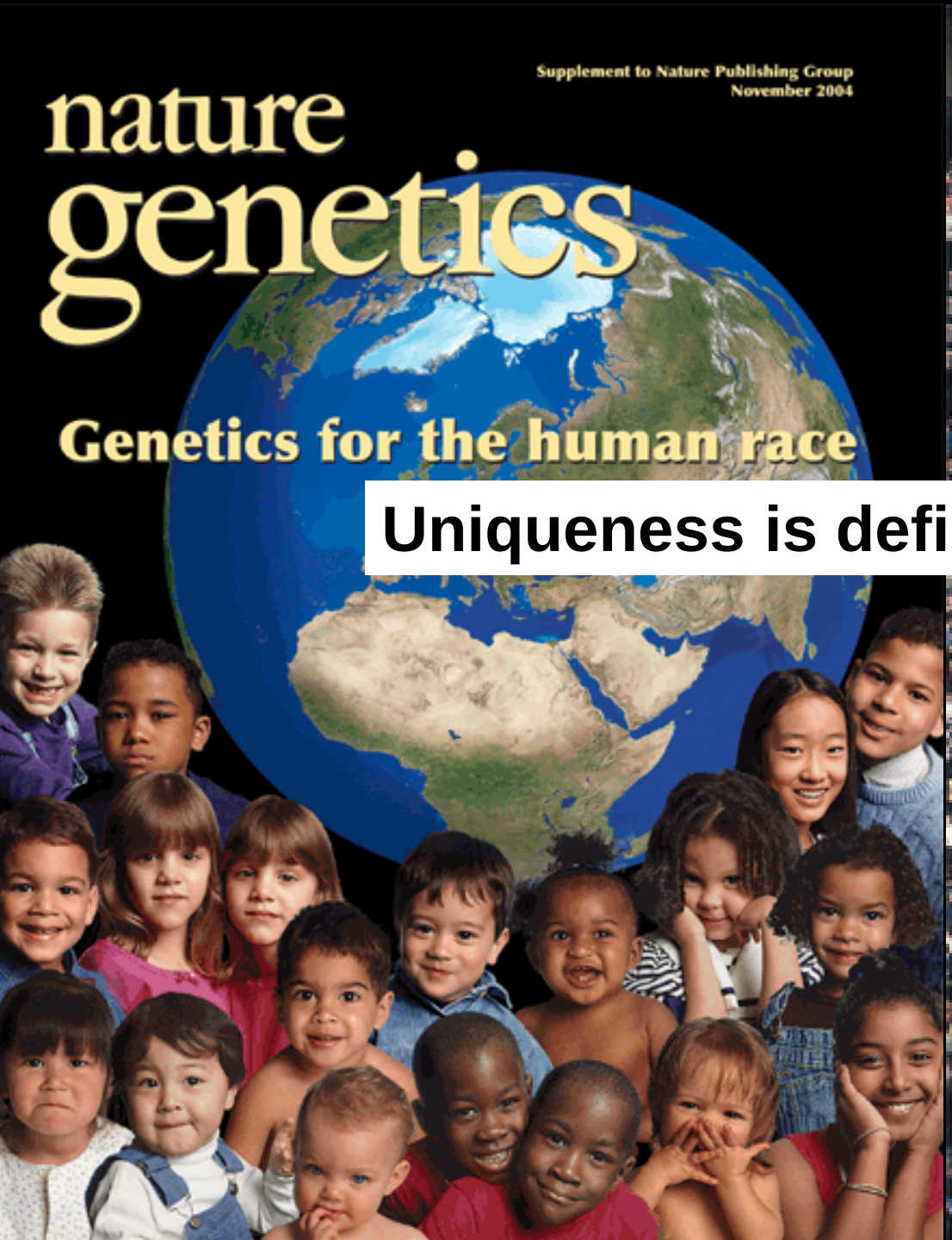
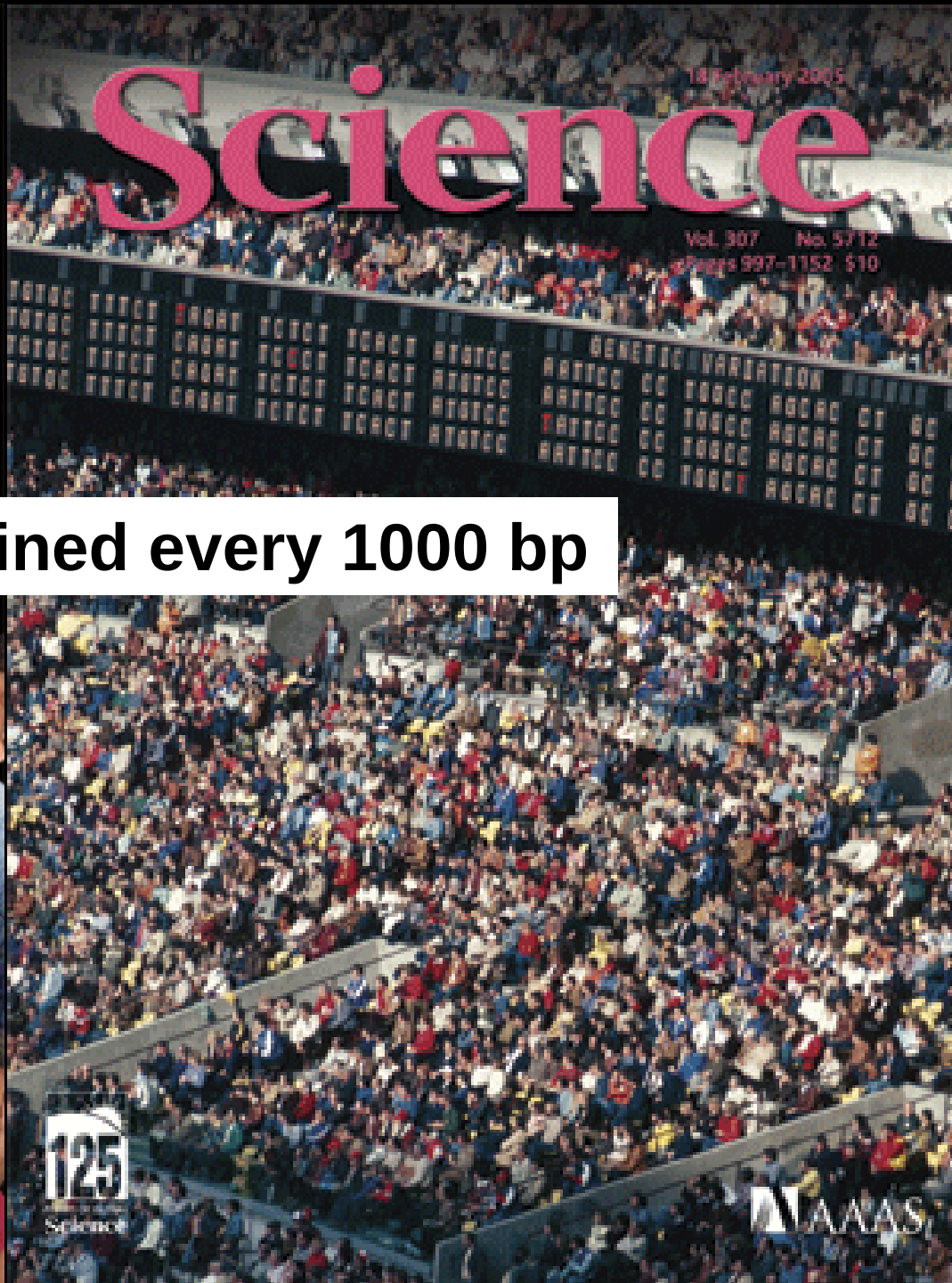
the human genome
Nuclear fission
Five-dimensional energy landscapes
Seafloor spreading
The view from under the Arctic ice
Career prospects
Sequence creates new opportunities

2001


16 February 2001
Science
Vol. 291 No. 5507
Pages 1145–1434 $9
THE HUMAN GENOME
American Association for the Advancement of Science

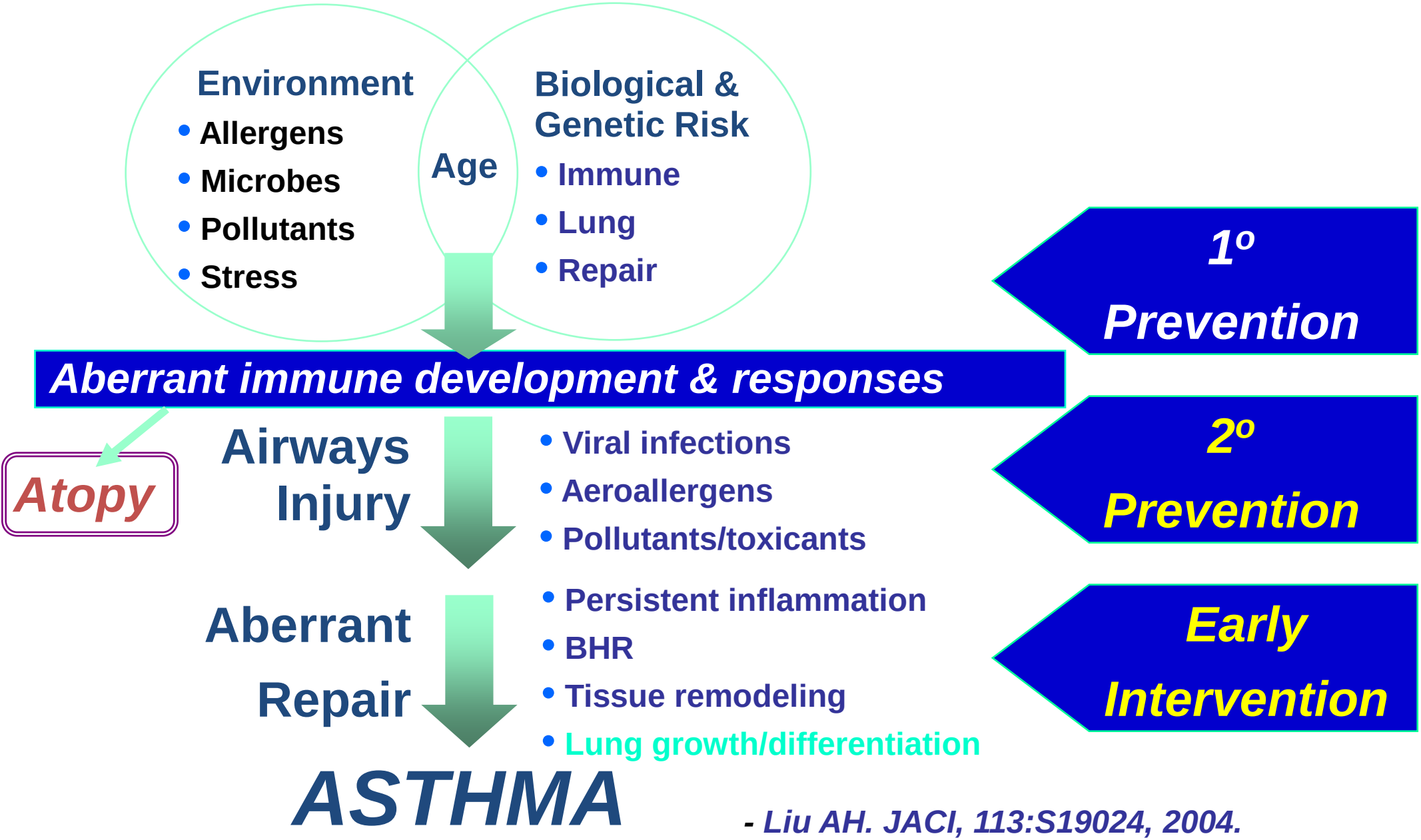

15 million polymorphisms
1 base pair variant/200 base pairs





Uniqueness is defined every 1000 bp

Early Intervention for Asthma Prevention



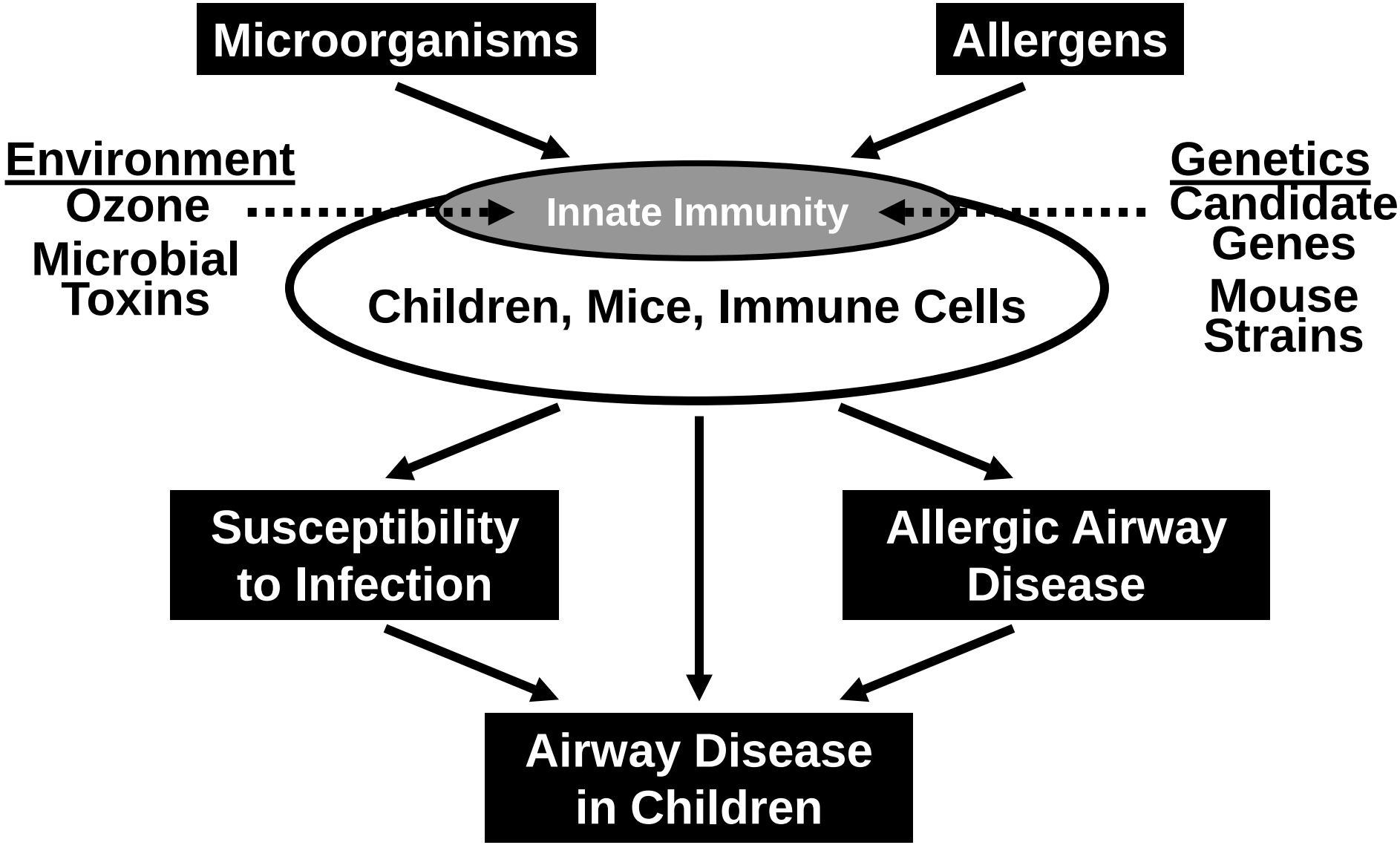
- *Liu AH. JACI, 113:S19024, 2004.*

How Do we Move Forward?

Guiding principles

- *Family history* is a strong predictive feature.
- *NIH guidelines* have helped set standard of care but application is limited.
- *Clinical monitoring* is the most practical method but may underestimate disease activity.
- *Genetic testing* is still in discovery stage.
- *Biomarkers* require careful validation before general clinical application.
- *Electronic medical records* facilitate summary of natural history.

NIEHS/EPA Childhood Environmental Health Center Grant:
The Environmental Determinants of Airway Disease in Children



Denver Center Projects

Project 1: Higher levels of *endotoxin exposure* cause persistent, problematic asthma and that *key environmental and genetic modifiers* contribute to endotoxin susceptibility and pathological asthmatic responses in children.

Project 2: *Ozone exposure* in the early postnatal phase alters *lung development* and modifies the *host immune response* to early life viral infection and allergen exposure, thereby contributing to the development of reactive airway disease.

Project 3: Expression of toll-like receptors in the lung are influenced by *environmental and genetic factors*, and the dynamic expression of toll receptors has profound effects on *lung host defense* and consequently the development of lung infections and allergic airway disease.

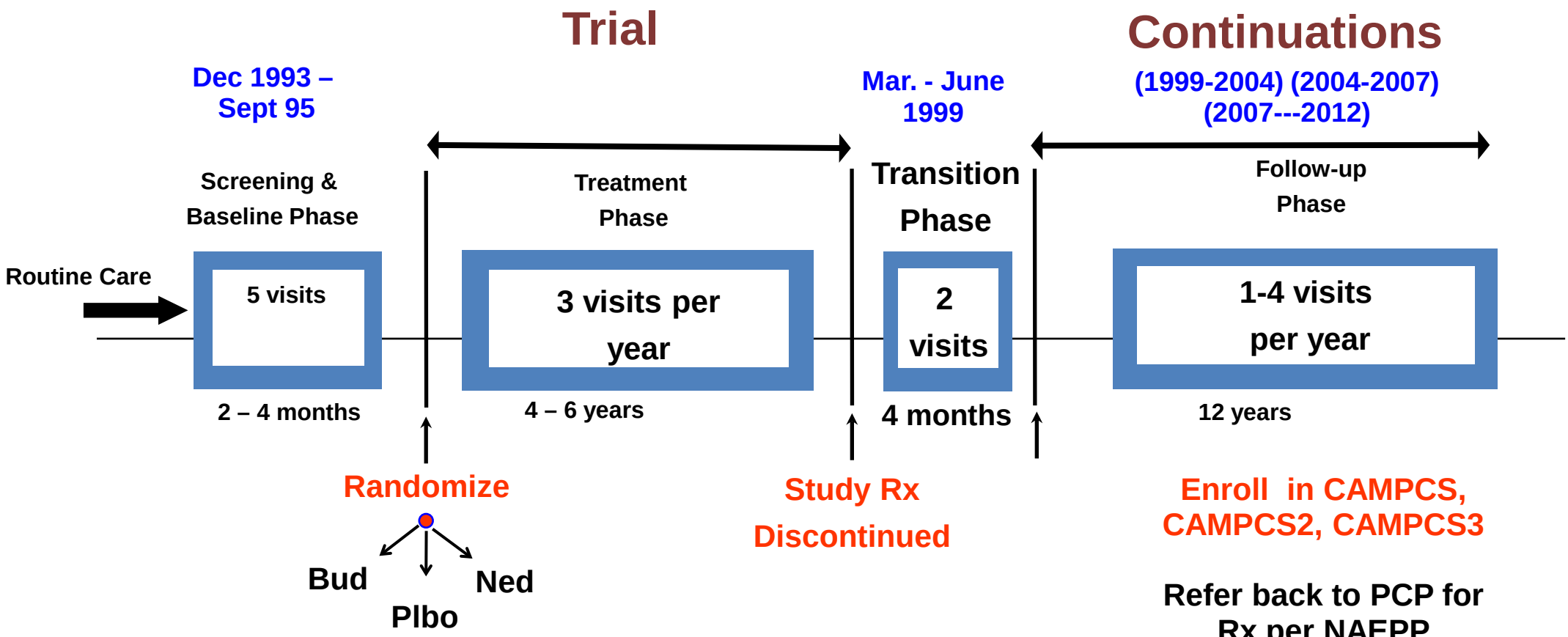
Community Outreach and Translation Core

- Investigators, practitioners, and community stakeholders
- Community Advisory Board: multi-disciplinary, multi-regional, multi-sectoral, dedicated, engaged, and appropriately opinionated
- Community engagement and community based participatory research
- Goal is to improve the health of children at risk

Project 1: CAMP Questions

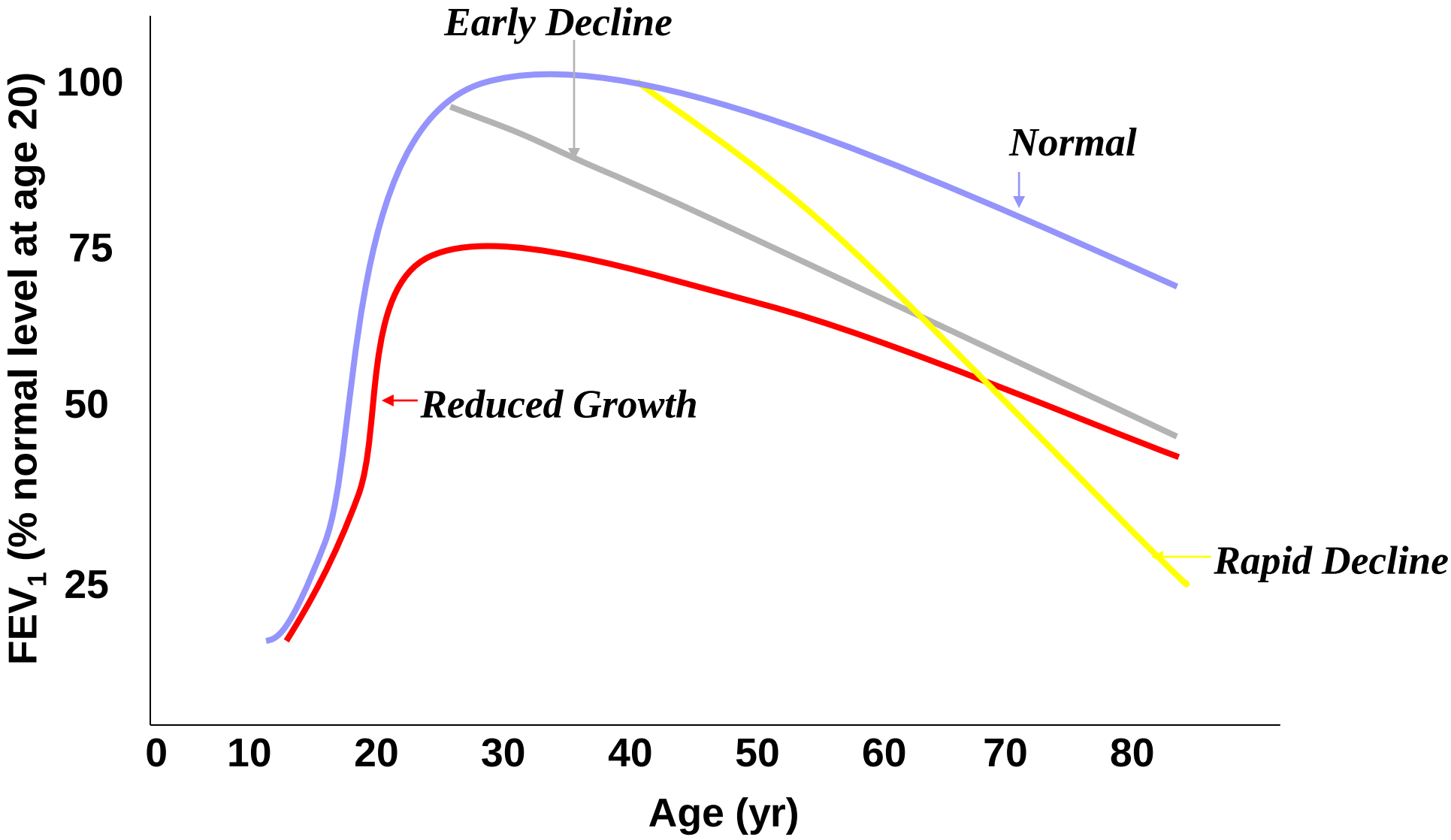
- Does home endotoxin exposure worsen asthma?
  - Obstruction
  - Inflammation
  - Twitchiness
  - Persistence
  - Severe attacks
- Does allergy + exposure amplify endotoxin's toxicity?
- Do genetic variants in the endotoxin recognition receptor alter endotoxin's effects on asthma?

CAMP Trial and Continuations



1,041 children 5-12 years of age
Mild to moderate persistent asthma

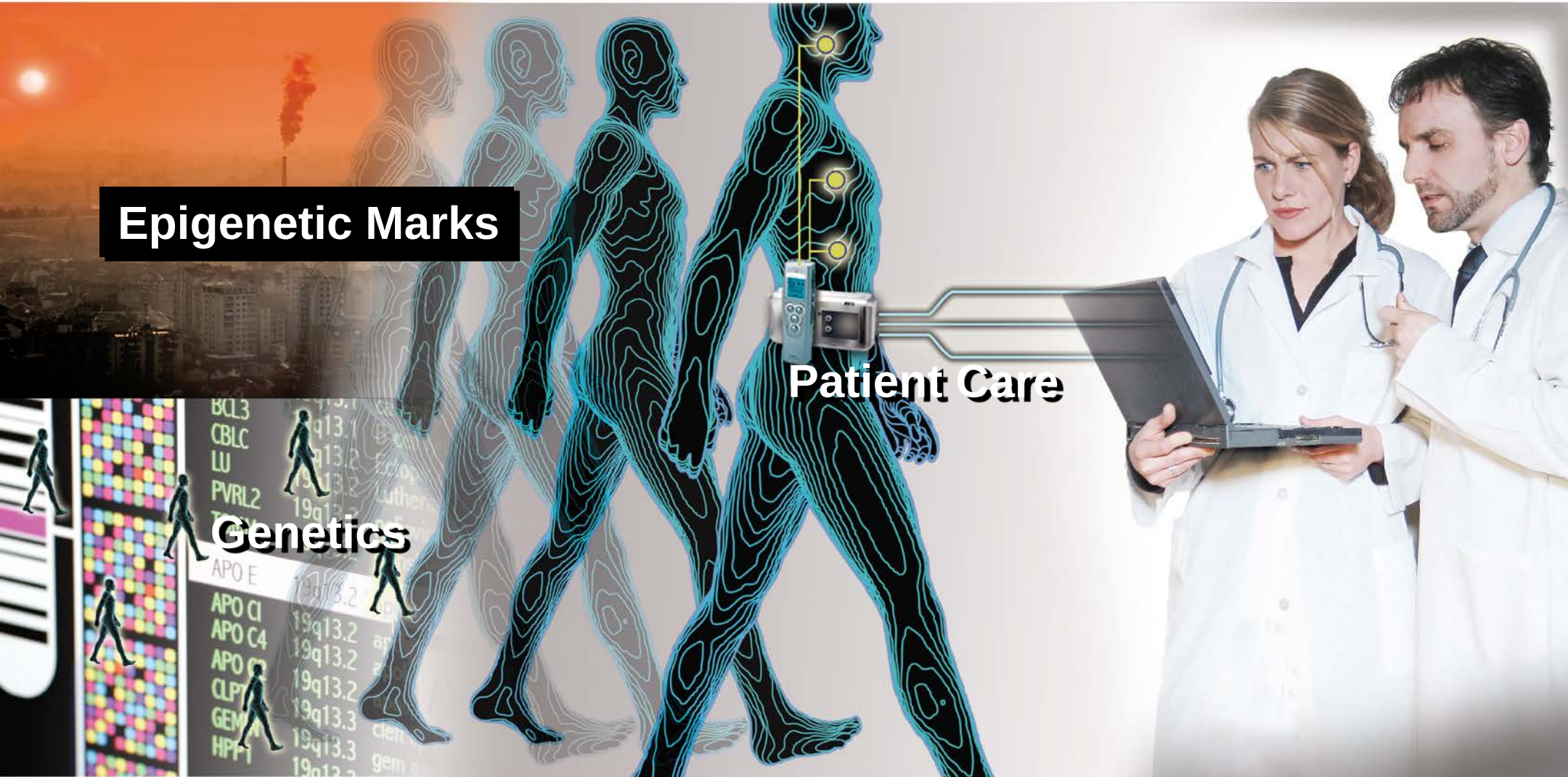
Rationale for Analysis of FEV_1 as Outcome: General Framework



Future Approaches to Asthma Management

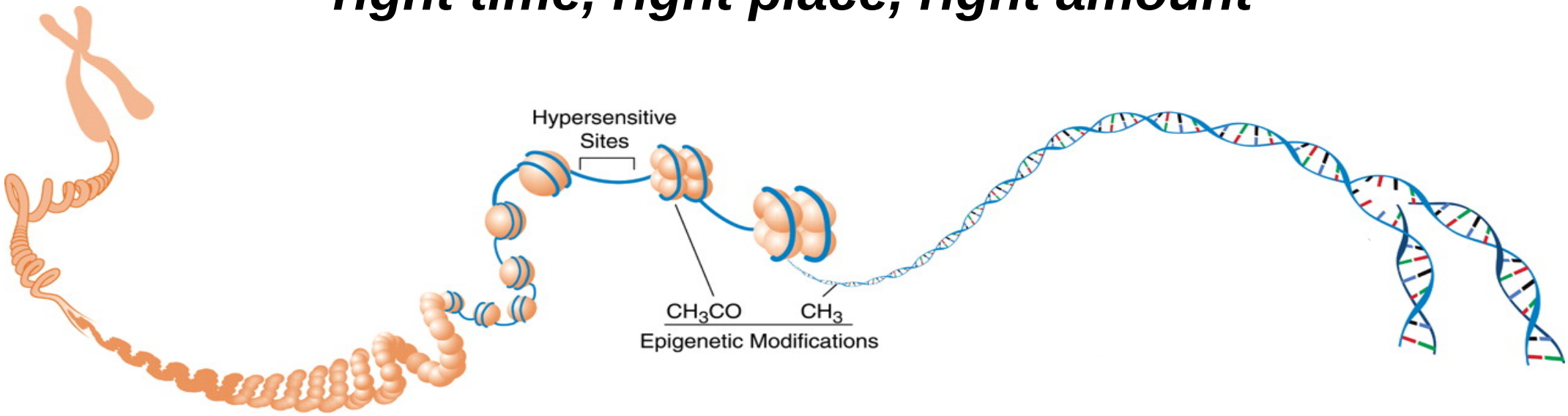
- **Early intervention** to prevent and control asthma
- Anticipate and **prevent asthma exacerbations**
- Apply **biomarkers** to monitor disease activity
- Use **genetics/epigenetics** to identify risk category for disease onset/severity
- **Immunomodulators** to alter course of disease

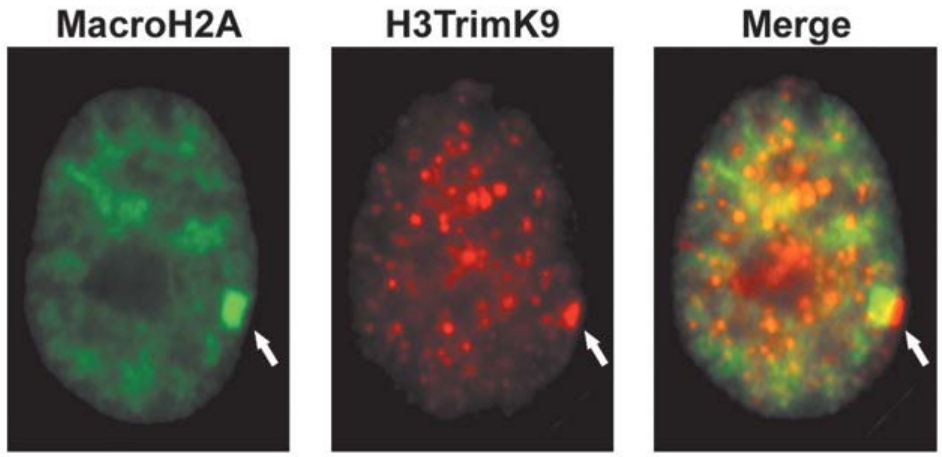
Genetics, Epigenetics, and Personalized Medicine



Epigenetics: Control of Gene Expression

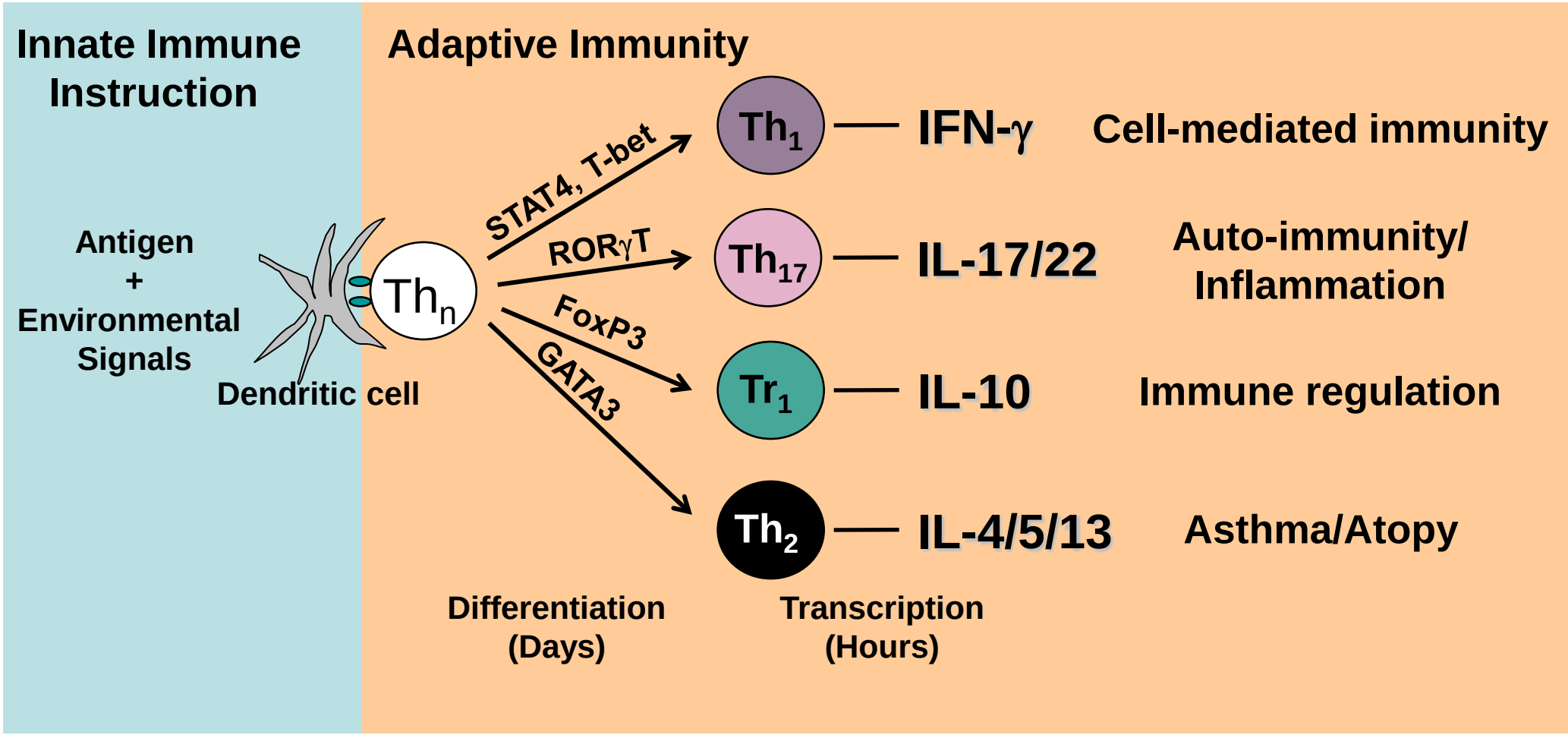
right time, right place, right amount



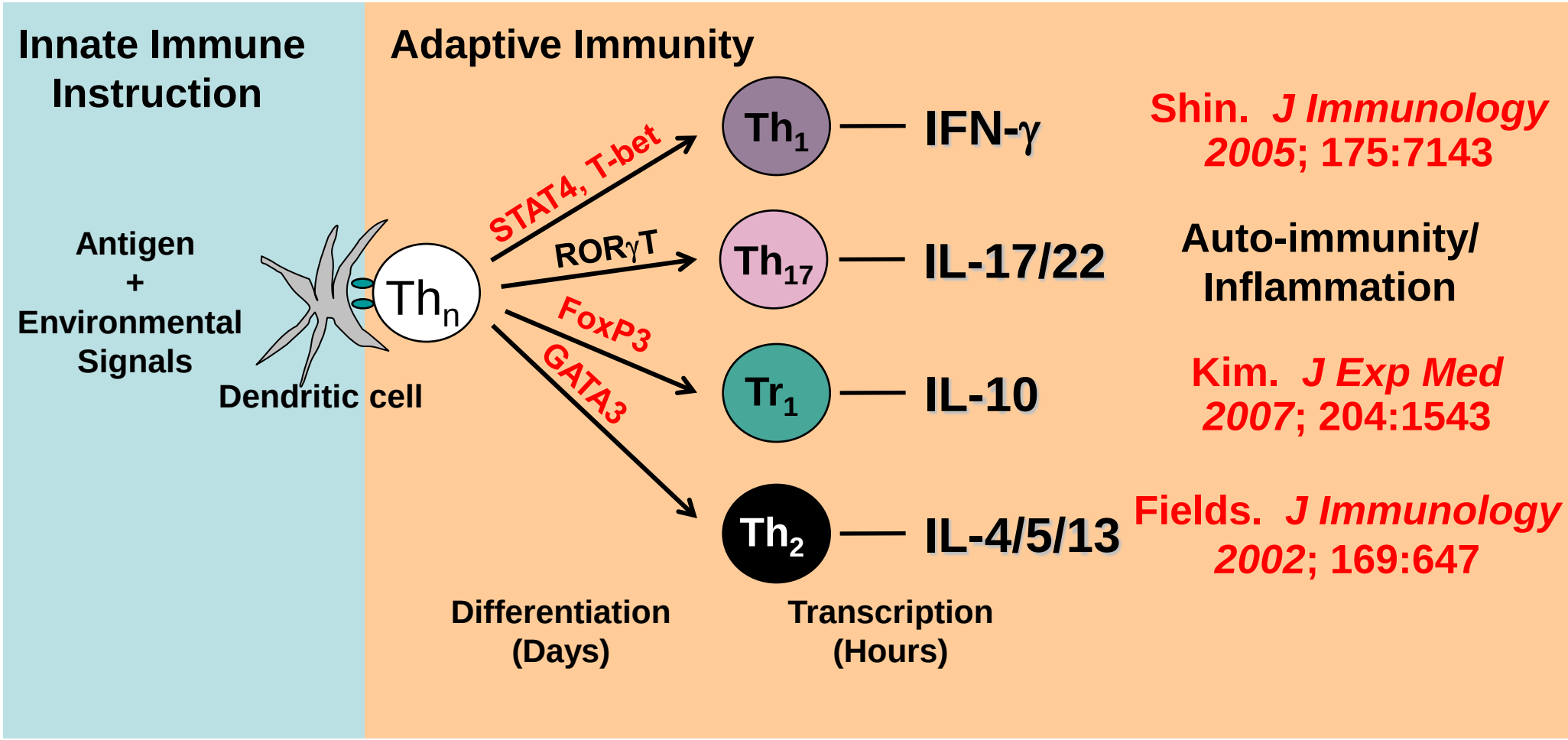


From ENCODE Consortium

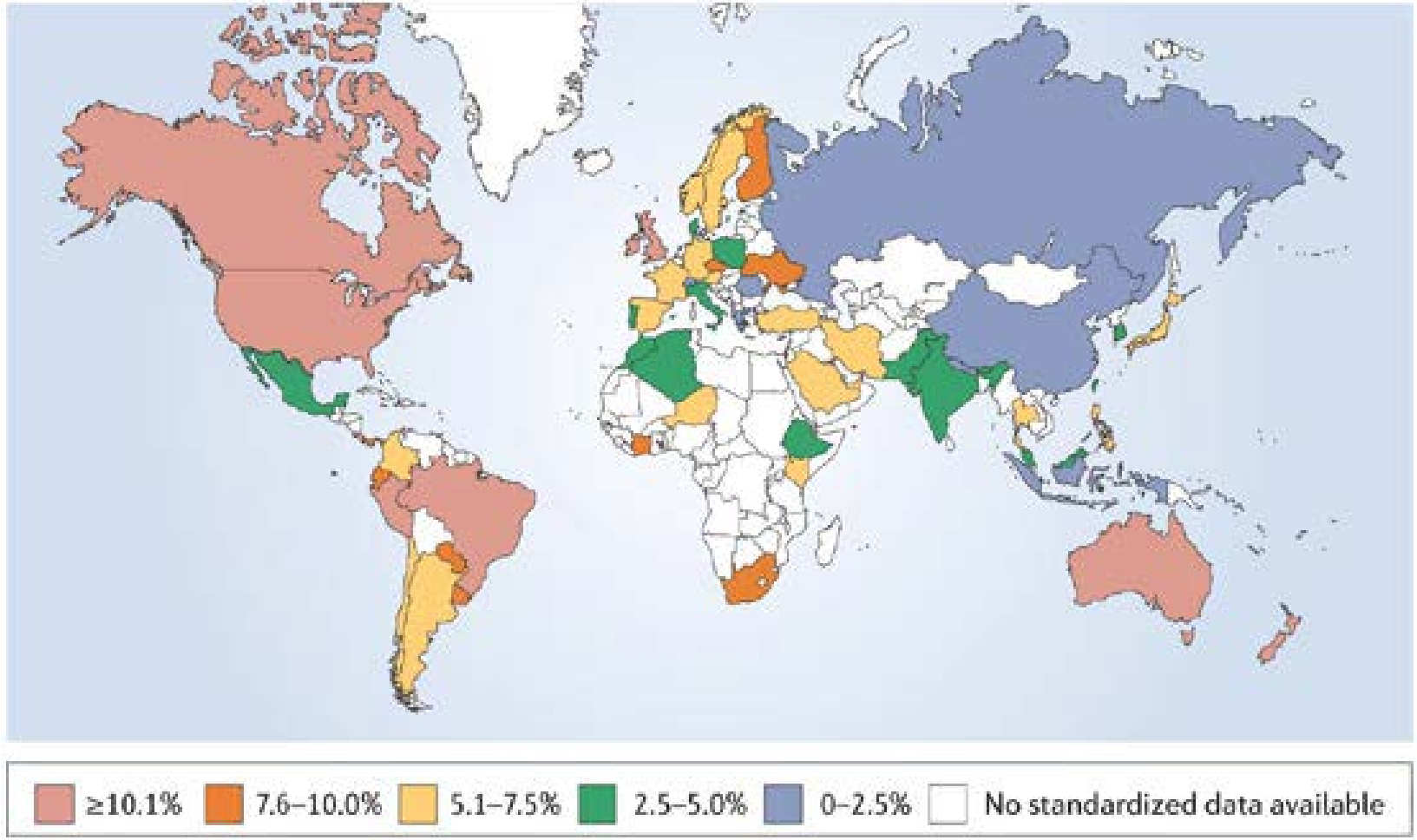
Epigenetics and Airway Immunology



Epigenetics and Airway Immunology

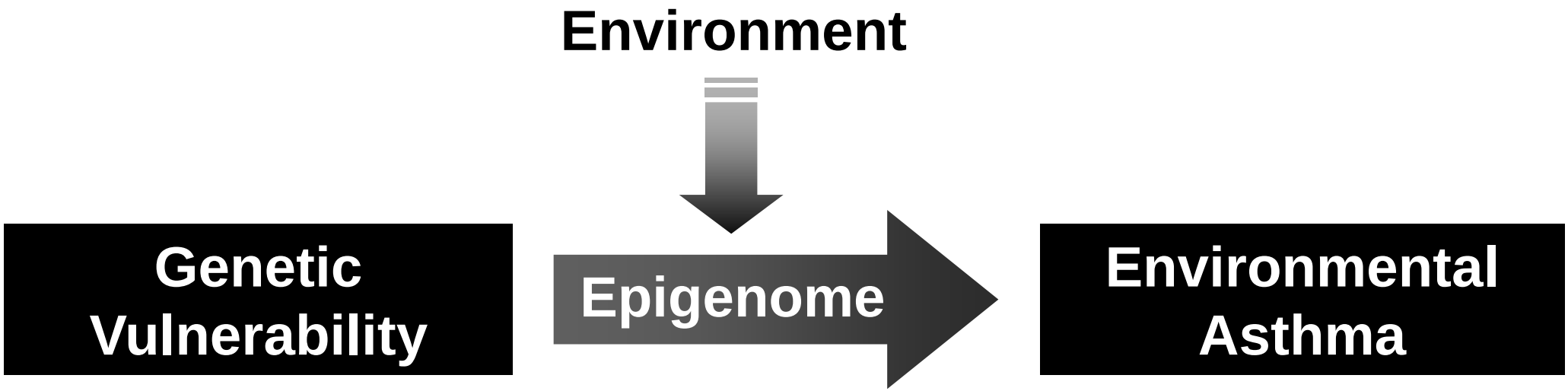


Asthma is Influenced by the Environment



Devereux. *Nature Reviews Immunology* 2006; 6:869

Etiology of Asthma

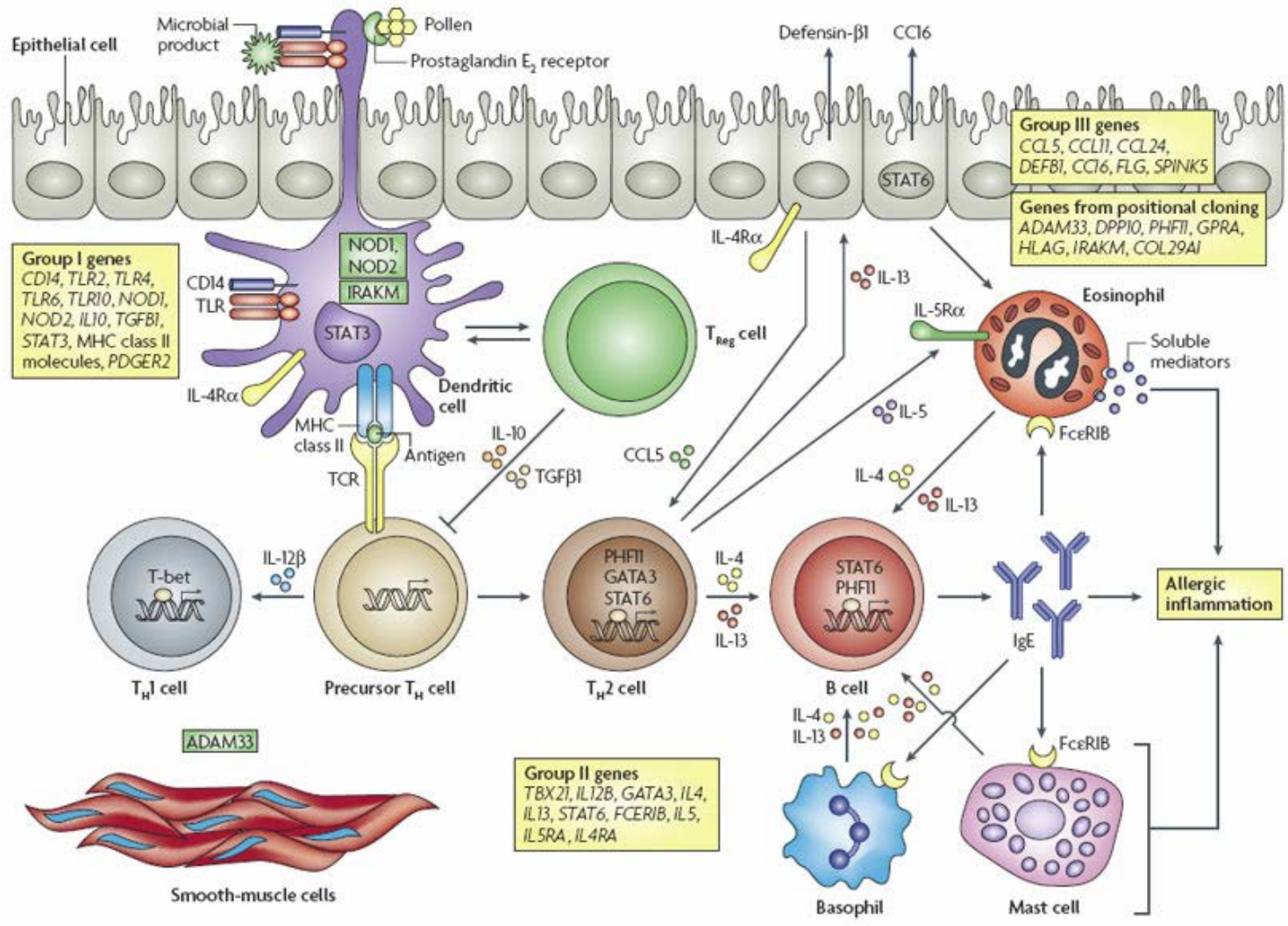


Epigenetics and Asthma

- non-Mendelian pattern of inheritance
- Influenced by the environment
- Affected by *in utero* exposures
- Alter/involve maturation of T cells

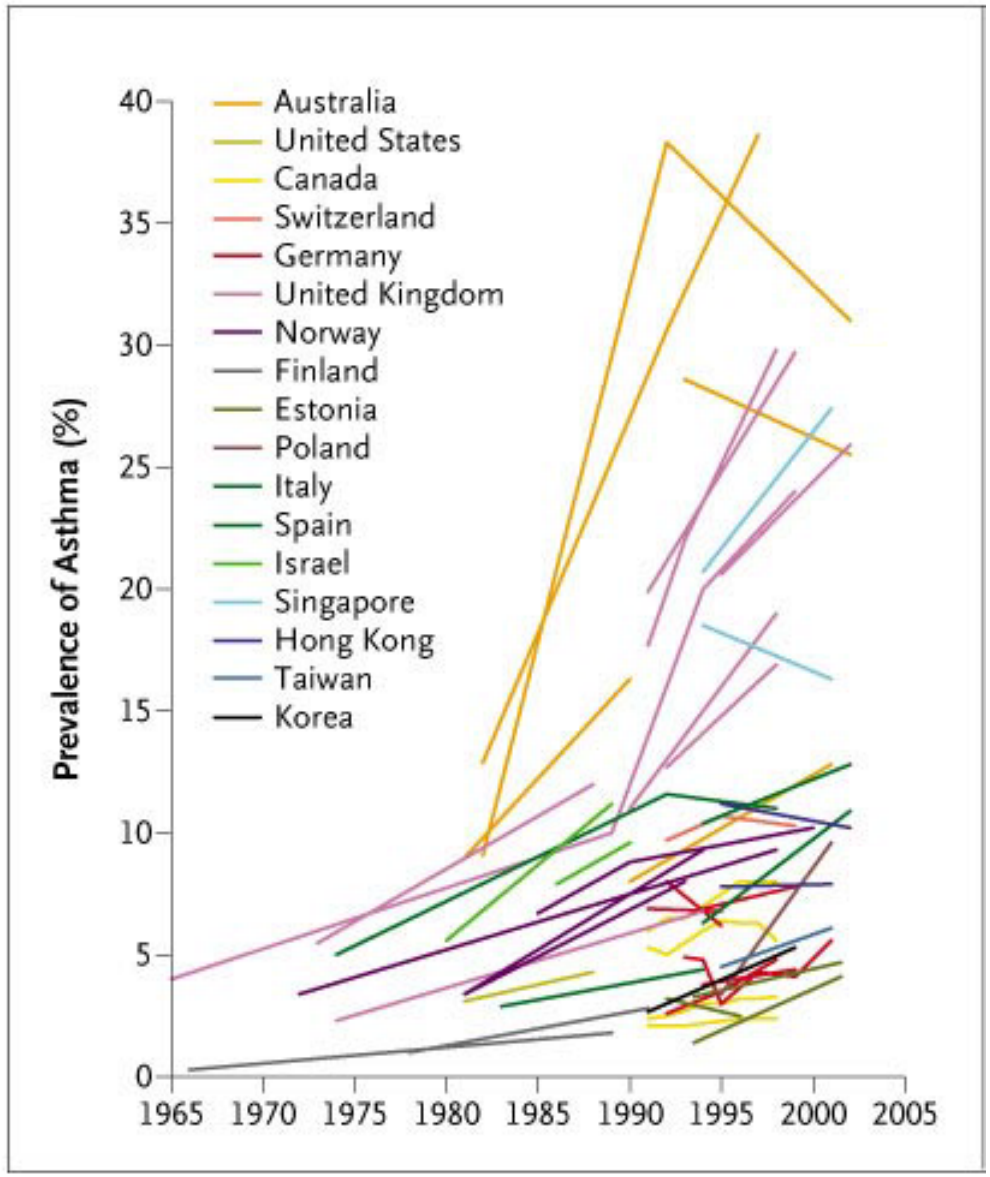
Susceptibility Genes in Asthma

[multiple genes – single disease]



Vercelli. *Nature Reviews Immunology* 2008; 8:169

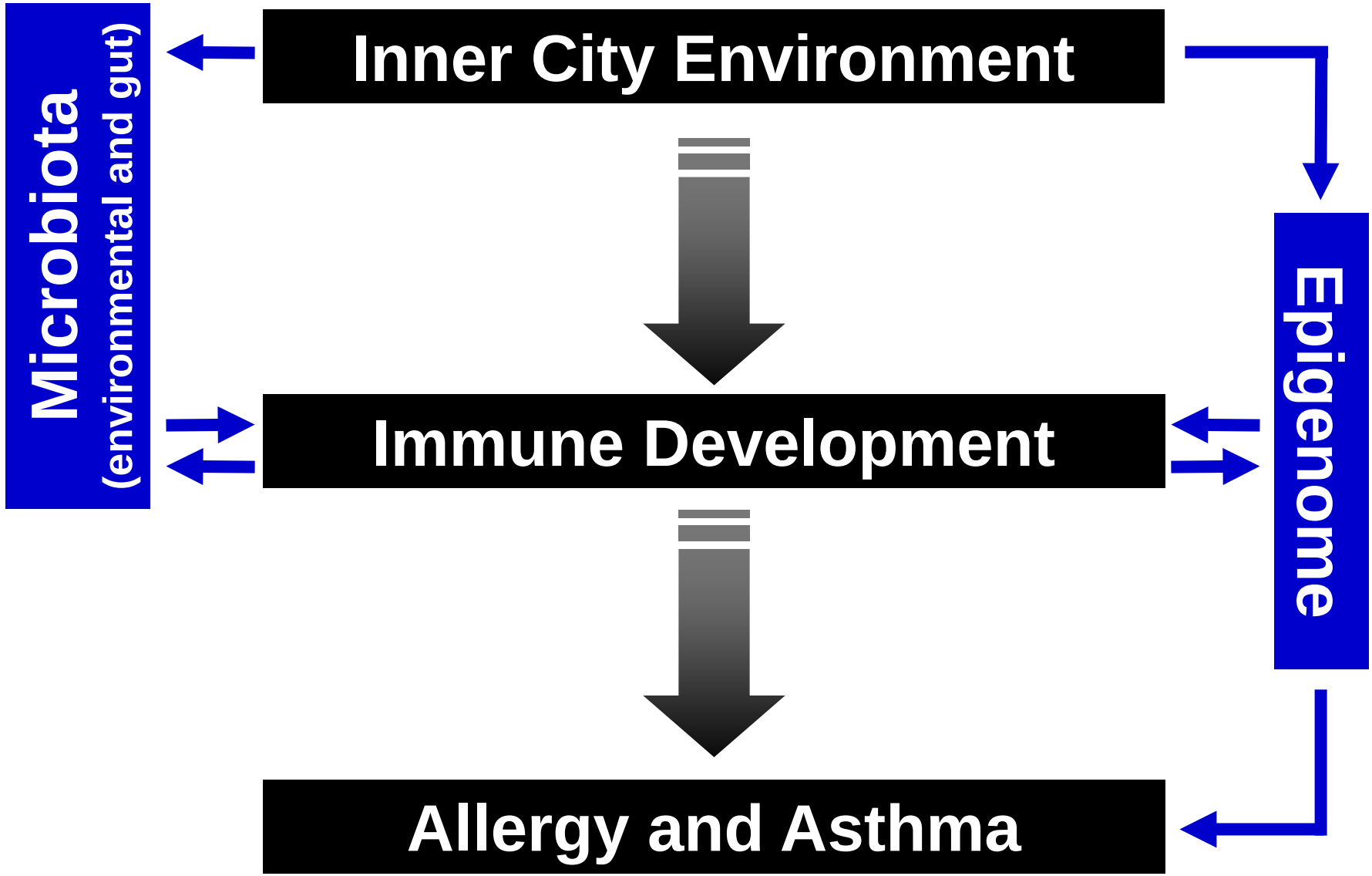
Asthma is a Major Public Health Problem



- **Affects millions of children and adults world-wide (over 30 million in the U.S.)**
- **More prevalent among children and minorities**
- **Cost of asthma continues to increase (> $10 billion annually in the U.S.)**

Eder. *NEJM* 2006; 355:2226

NIAID Inner City Asthma Consortium



Denver Public School Asthma Program

A collaboration of community partners creating school-based asthma programs

National Jewish Health™
Science Transforming Life®

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DG DANIEL GRAHAM FOUNDATION

DENVER HEALTH
Level One Care for ALL

The Children's Hospital

COLORADO ASTHMA COALITION

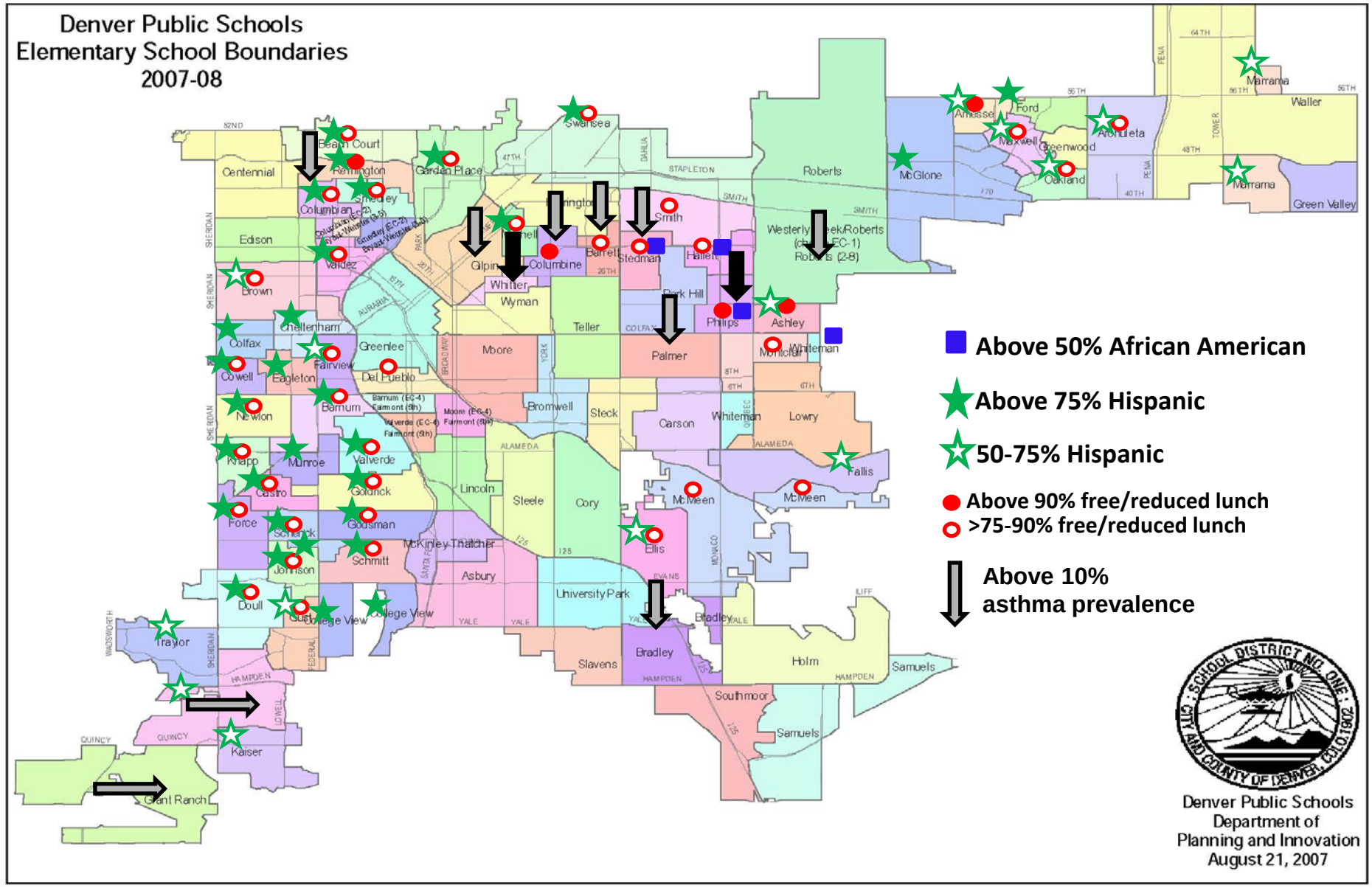
Cancer, Cardiovascular Disease and Pulmonary Disease Competitive Grants Program

STATE OF COLORADO 1876

Colorado Department of Public Health and Environment

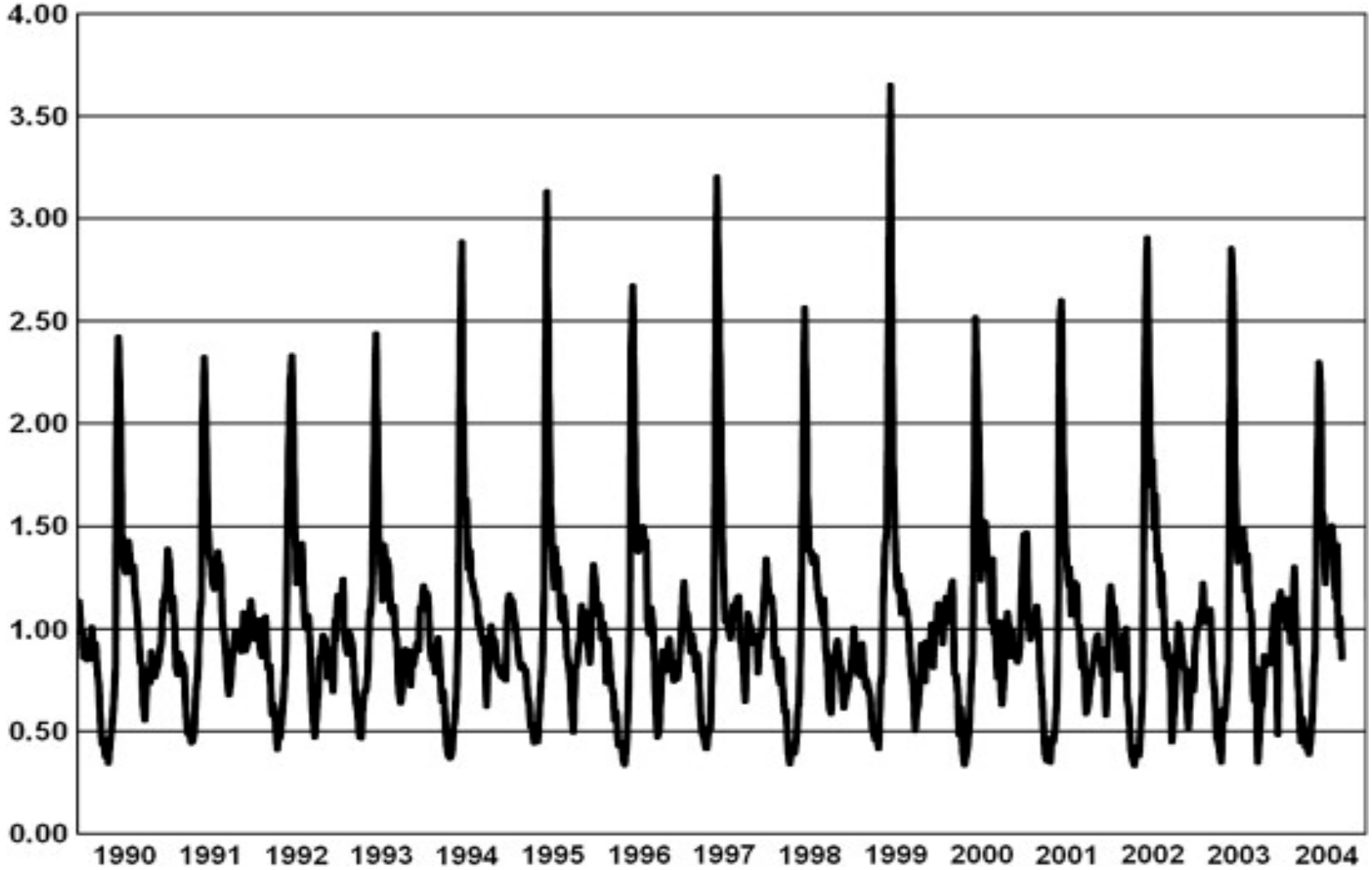
AMERICAN LUNG ASSOCIATION. of Colorado

DPS Elementary Schools Asthma Disparaties



Hospitalizations for Asthma in Children: *Canada*

*** 20 - 25% of all hospitalizations in Canada for childhood asthma exacerbations occur in September**



Sears MR, Johnston NW. JACI 2007;120:526-9.

Project 2

Environmental Determinants of Early Host Response to RSV and Allergen

Overall Objective

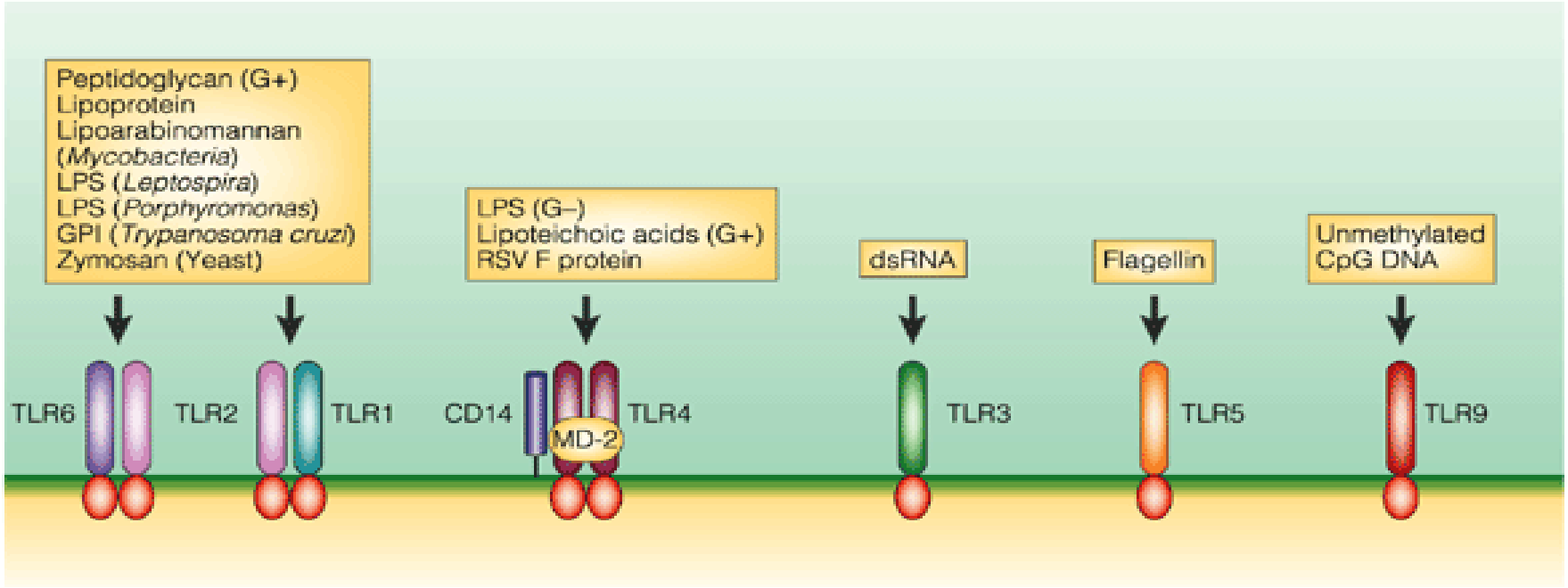
Define how reactive airway disease (asthma) develops in response to common triggers (RSV, Allergen), influenced by environmental factors (Ozone, Endotoxin) in early life

Specific Aims

- Determine the effects of ozone on *postnatal lung development, innate immunity* (TLRs expression) and *airway function*.
- Define how ozone influences the *early postnatal response to RSV and HDM allergen*, and determines the development of asthma-like phenotype.
- Determine how *endotoxin* (bacterial air contaminant) influences the *development of asthma* by modifying the early response to RSV and HDM allergen, following postnatal ozone exposure.

Toll-like Receptors

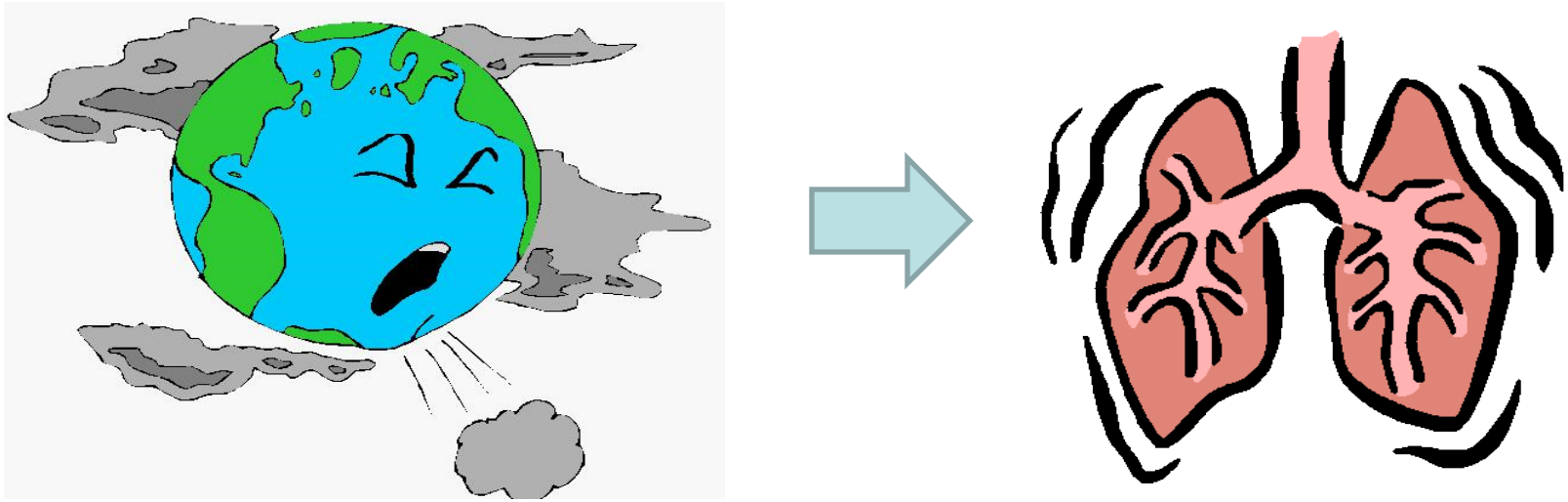
- TLRs (pathogen recognition receptors)



Nature Reviews | Immunology

Project 3:
Environmental Determinants of Host Defense in Mice

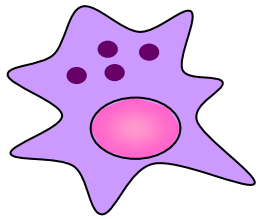
The overall goal of this project is to understand how and why air pollution alters lung host defense.

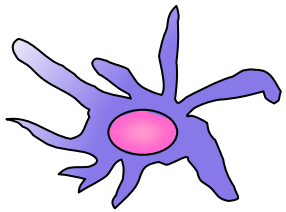


Specific Aim 1

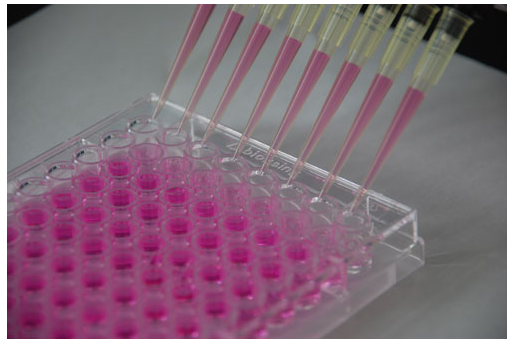
Determine the effect of *in vitro* exposures to ozone and/or PAMPs on the expression of TLRs in murine macrophages and DCs.

- 129/SvIm
- A/J
- BALB/c
- C57/B6
- DBA/2J





Ozone
PAMPs
Ozone + PAMPs



- **TLR expression**
- **TLR distribution**
- **Cytokine production**

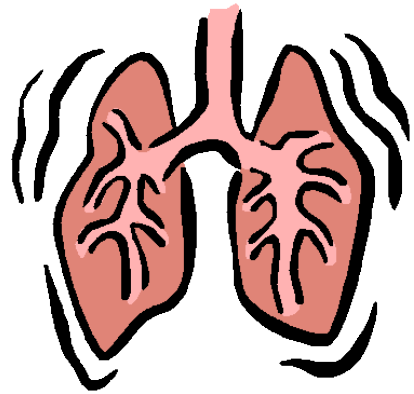
Specific Aim 2

Determine the effect of *in vivo* exposures to ozone and/or PAMPs on the expression of TLRs in mouse lungs.

Aim 1 Data

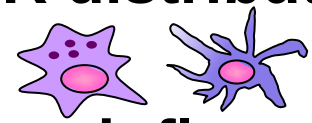
129/SvIm
A/J
BALB/c
C57/B6
DBA/2J

Ozone
PAMPs
Ozone + PAMPs



TLR expression

TLR distribution



Lung inflammation

AHR

Specific Aim 3

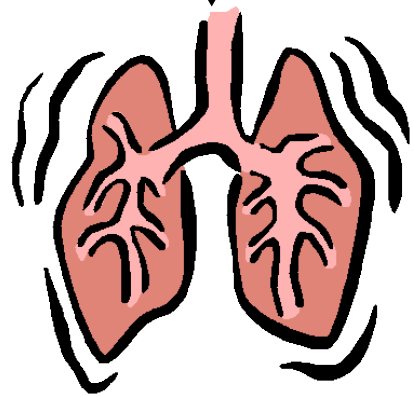
Determine the effect of *in vivo* exposures to ozone and/or PAMPs on susceptibility of mice to lung pathogens.

Aim 2 Data

Ozone
PAMPs
Ozone + PAMPs

129/SvIm
A/J
BALB/c
C57/B6
DBA/2J

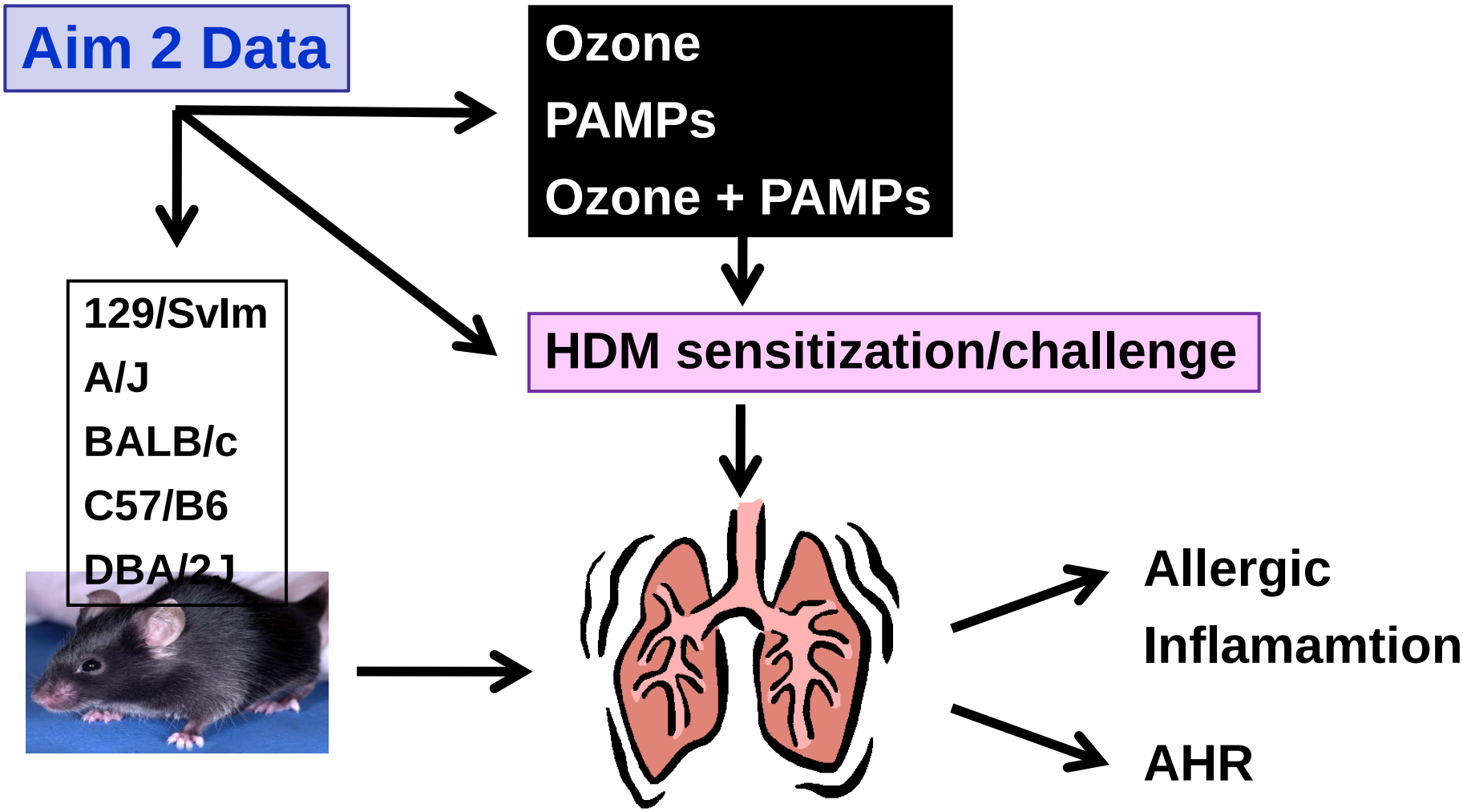
Lung pathogens



Morbidity
Pathogen Clearance
Lung inflammation
AHR

Specific Aim 4

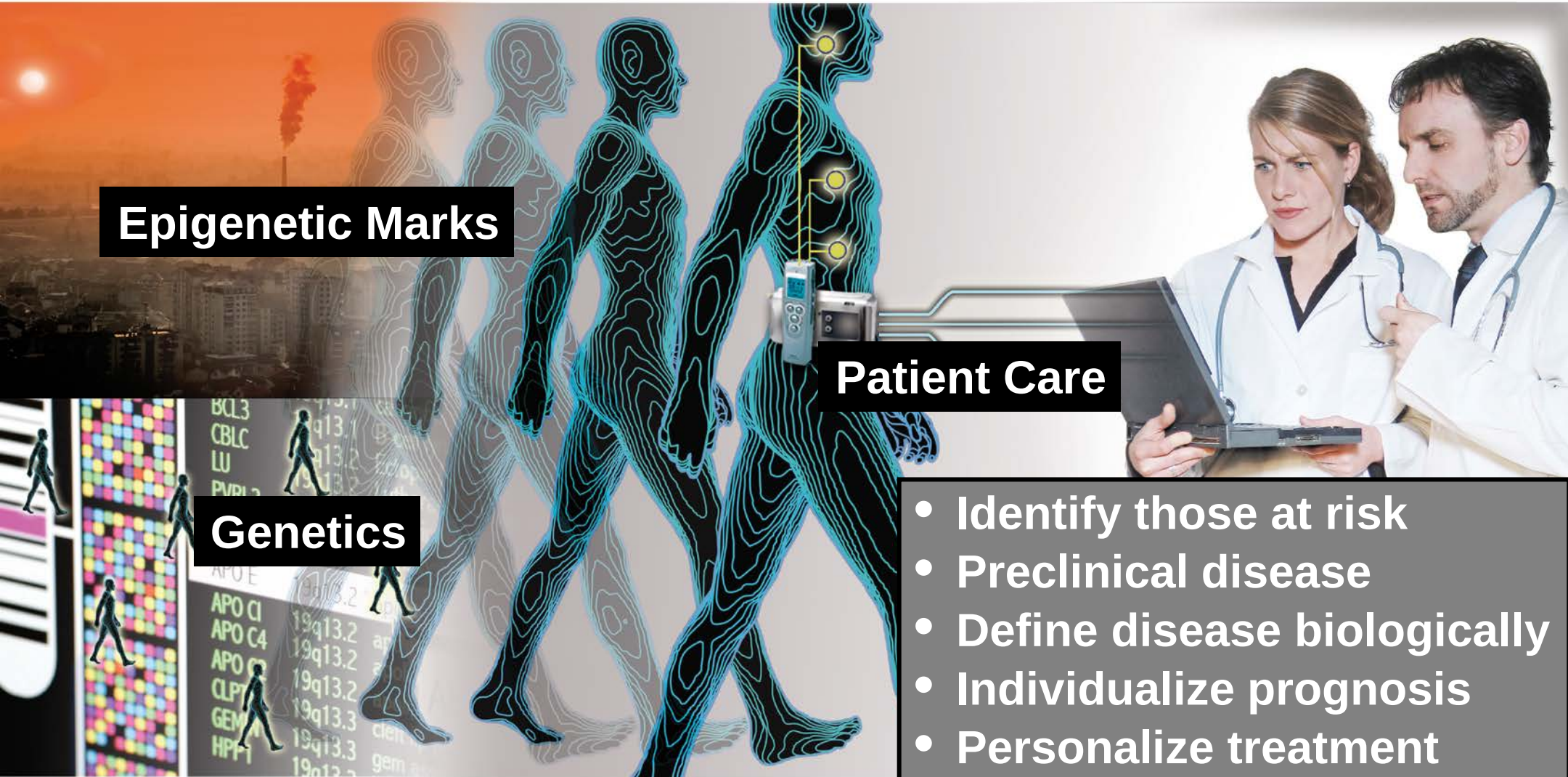
Determine the effect of *in vivo* exposures to ozone and/or PAMPs on house dust mite (HDM) induced allergic airway disease in mice.



Anticipated Significance and Impact

- Airway disease in children is a major *public health problem*
- *Air pollutants* exacerbate airway disease in children and enhance the susceptibility to infectious agents
- Children are more *vulnerable* to air pollution (lung development, immune development, and increased exposures)
- Innate immune receptors represent primary forms of *host defense* and are altered by air pollution
- Our *center* will address some of the basic precepts about asthma – *in utero* exposures, developmental biology, immune responsiveness**,** community impact, and outreach and education

Genetics, Epigenetics, and Personalized Medicine



- Identify those at risk
- Preclinical disease
- Define disease biologically
- Individualize prognosis
- Personalize treatment

Contact Information

Communication sources

- Websites:

  www.nationaljewish.org/cehc

  NIEHS/EPA CEHC web site
- Director: david.schwartz@ucdenver.edu
- Co-Director: szeflers@njhealth.org
- Community Outreach: cicuttol@njhealth.org